Demystifying Attention Deficit Hyperactivity Disorder

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Understanding ADHD
Two children

- Peter

- Restless and fidgety since birth.
- Impulsive.
- Inattentive, poor sustained focus.
- Diagnosed ADHD age 6

- Susan

- “Hyper hyper”.
- Physically impulsive.
- Highly distractible.
- Struggling at school.
- Diagnosed with ADHD age 6.

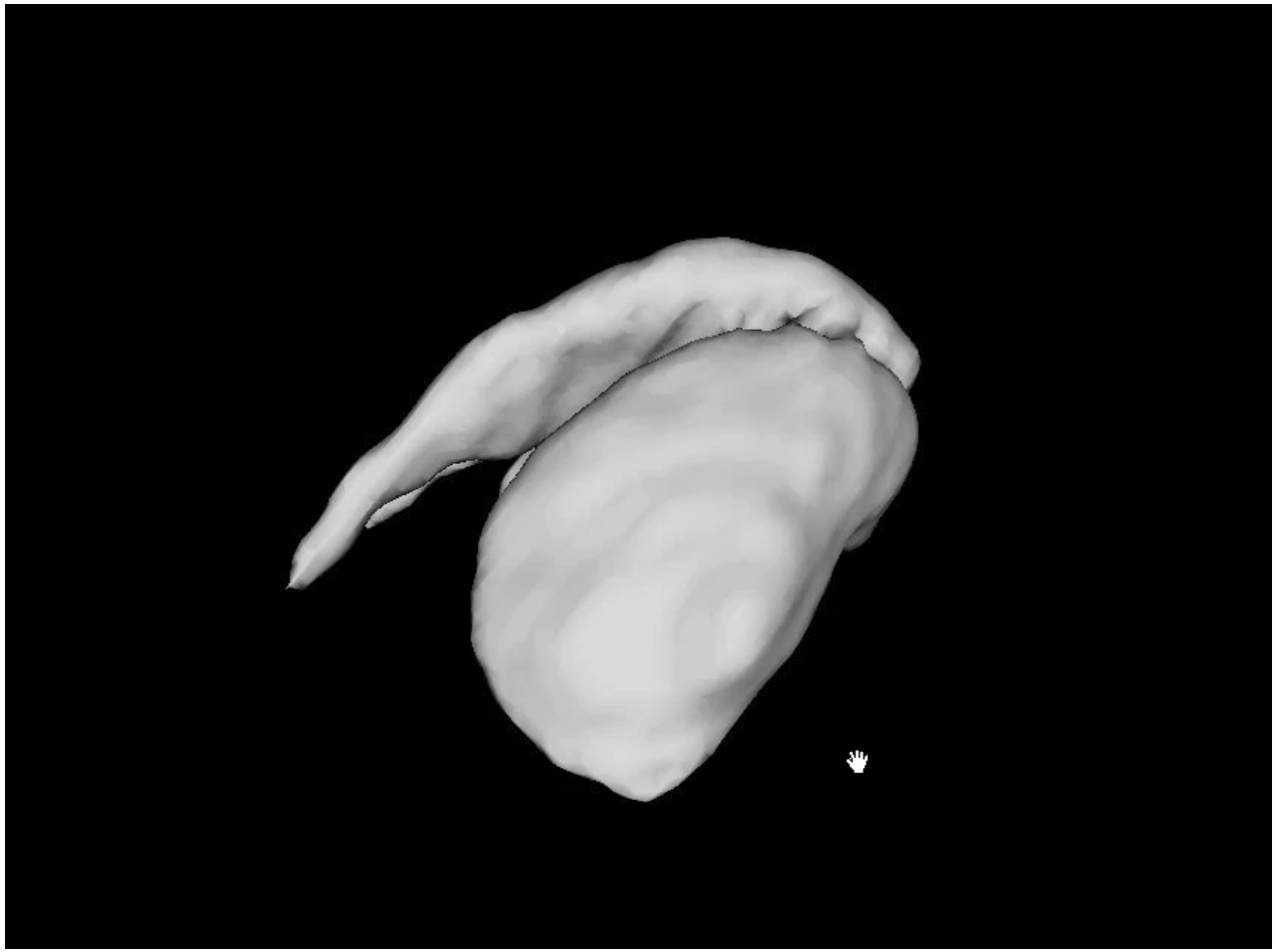
What's going on in the brain?

Questions

- Is brain development atypical in childhood ADHD?

- Are anomalies fixed or dynamic?
  1. Childhood ADHD and the striatum
  2. The adult outcome of ADHD and the cortex
  3. Adult ADHD and white matter tracts

The striatum= caudate + putamen (globus pallidus not included)



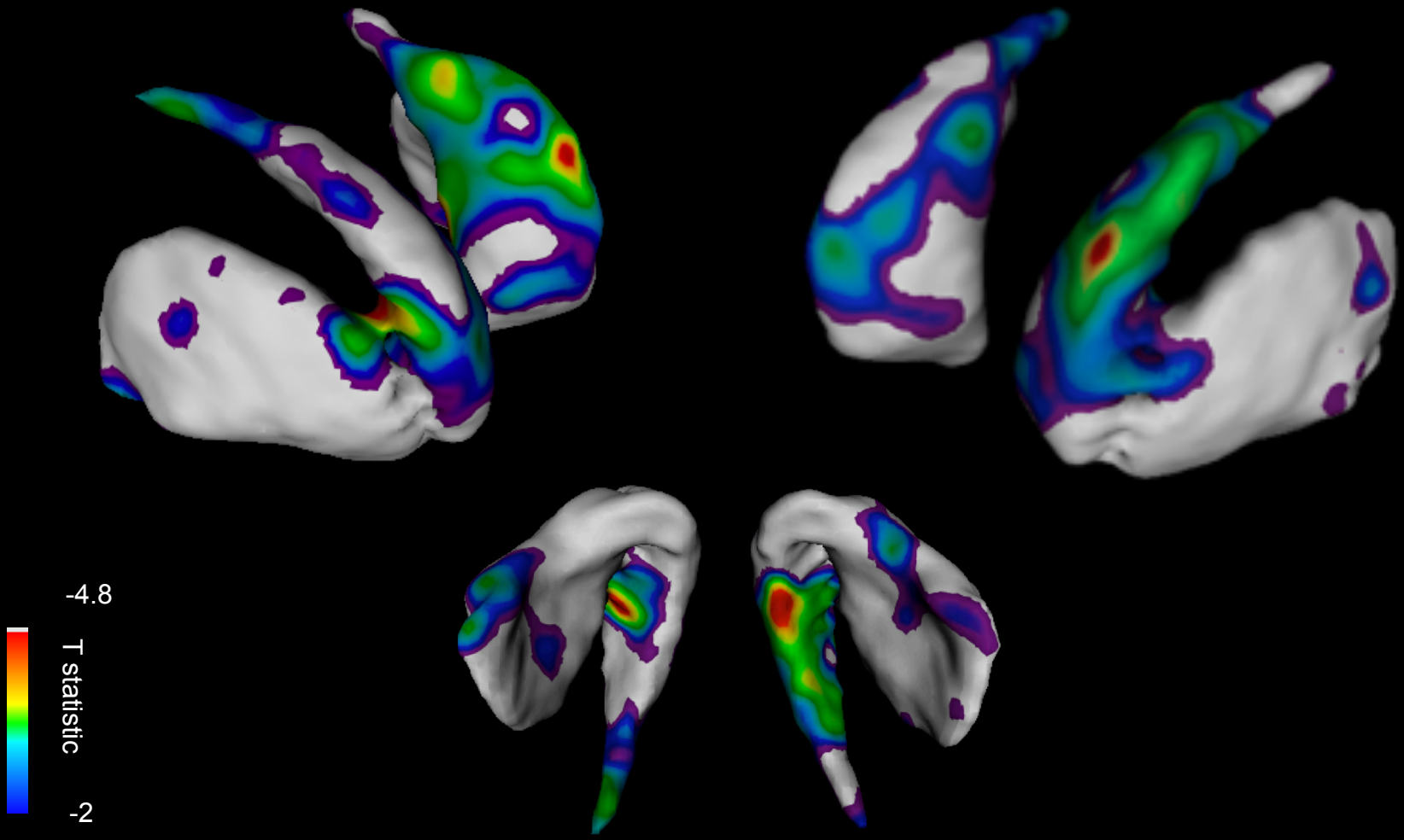
Childhood ADHD and the striatum.

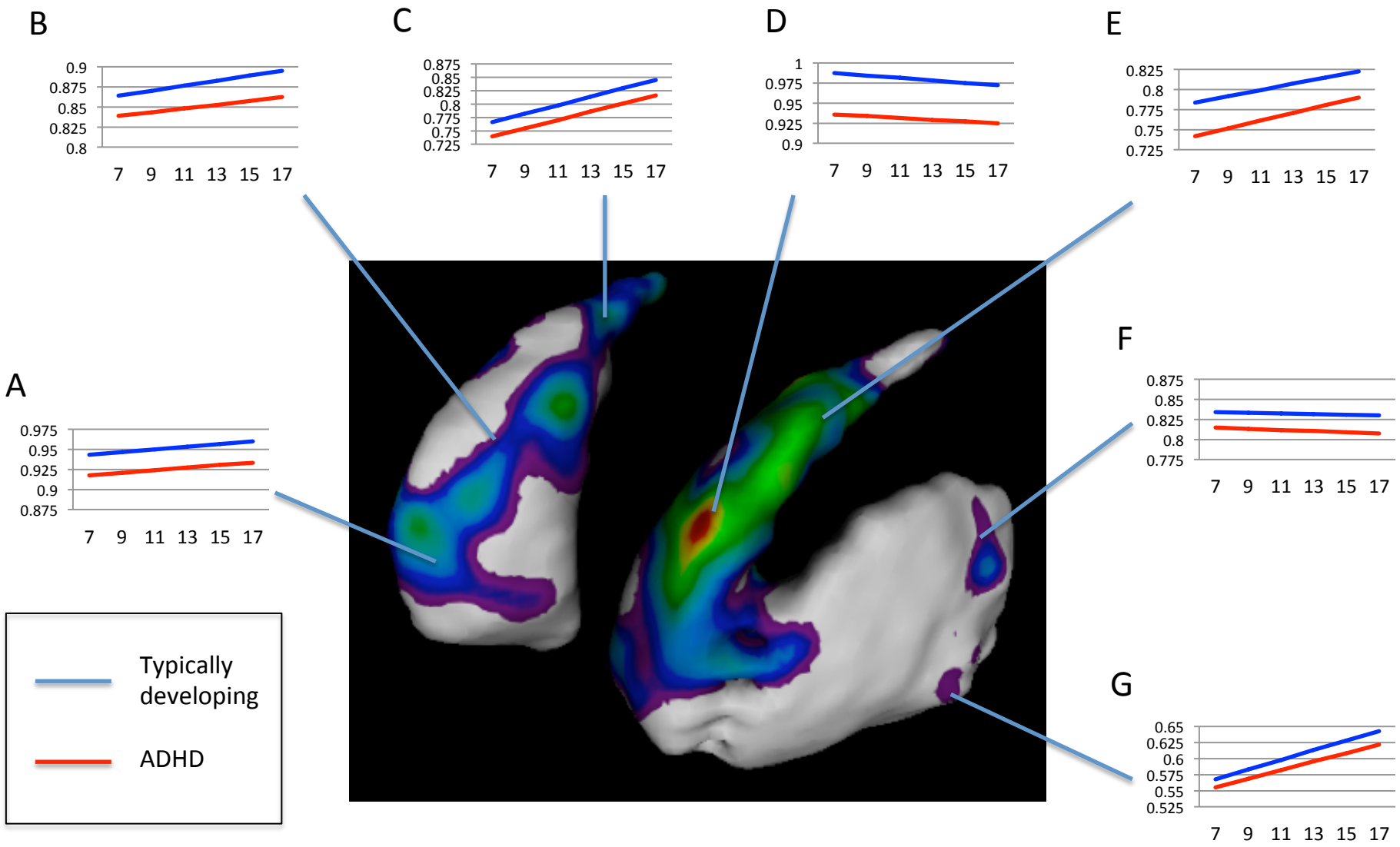
(Shaw et al, JAACAP 2014; Raznahan, Shaw et al, PNAS 2014,)

- Previous cross-sectional studies: striatum is smaller in ADHD (Nakao et al 2012)

- What about its development?
  - 270 children with ADHD, 270 controls; total of 869 scans (50% had repeated scans)
  - Defined striatal surfaces and mapped trajectories (linear mixed models; adjusted for multiple testing)

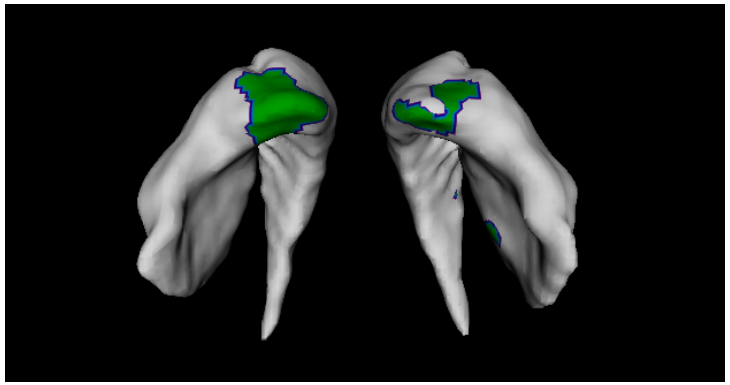
Surface based analyses: baseline differences



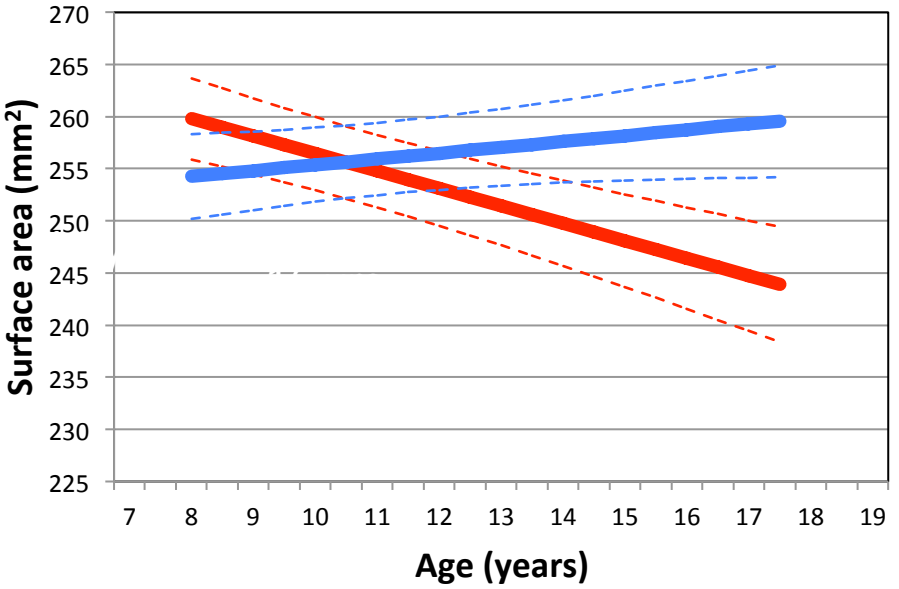


Trajectories at vertices throughout the striatum.

Where do trajectories differ in childhood ADHD?



Regions where there was a significant diagnostic difference in trajectories of surface area development (adjusted $p<0.05$)



Slope difference $t=5.6$, $p<0.00001$
Effect size 0.91 (CI: 0.79 to 1.03)

(Shaw et al, Under review)

Summary

- Fixed decrease in caudate/putamen surface area in ADHD

- Dynamic, progressive contraction of the ventral striatal regions while symptomatic
  - Ventral striatum receives limbic input: mediates reward processing
  - Hypoactive during anticipation of rewards (Shaw et al 2014)

Adult outcome in ADHD

Adult outcome

- **Peter**

- Parents agreed on medication and had close links with pediatrician and support groups.
- School instituted behavioral management plans.
- Symptoms improved during middle school.
- By age 16, no symptoms.
- Doing well academically, planning to go to college.

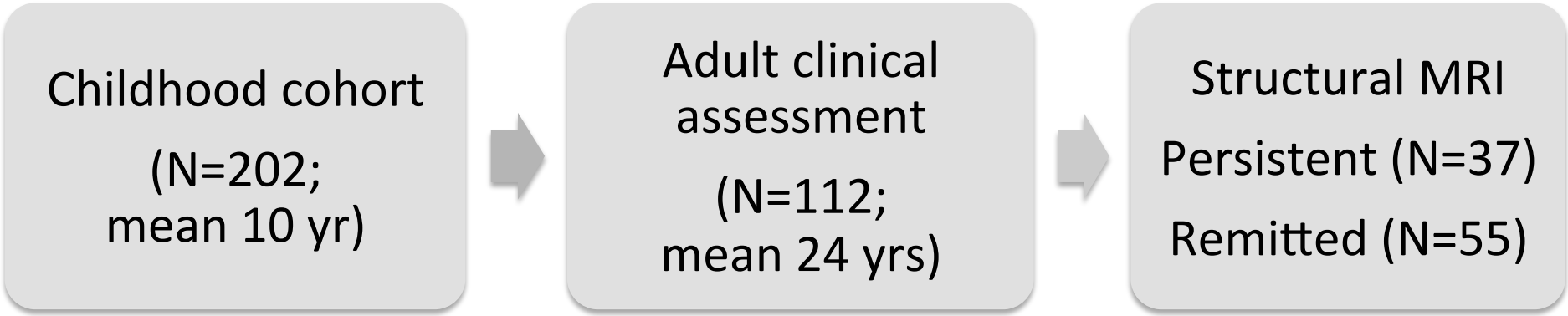
- **Susan**

- Parents initially did not want medication.
- Began ritalin age 9 and had a poor response. Second and third line medications failed.
- Struggled at school.
- Never received behavioral treatment.
- Poor peer relations and few links with healthcare systems.
- Had marked ADHD symptoms at age 16.

Full remission ~30%
Partial remission ~40%

Persistent ~30% (full syndrome)

Study 2:
Developmental trajectories and adult outcome



Hypothesis : **Adult** outcome is underpinned by different trajectories

Remission → convergence to typical development

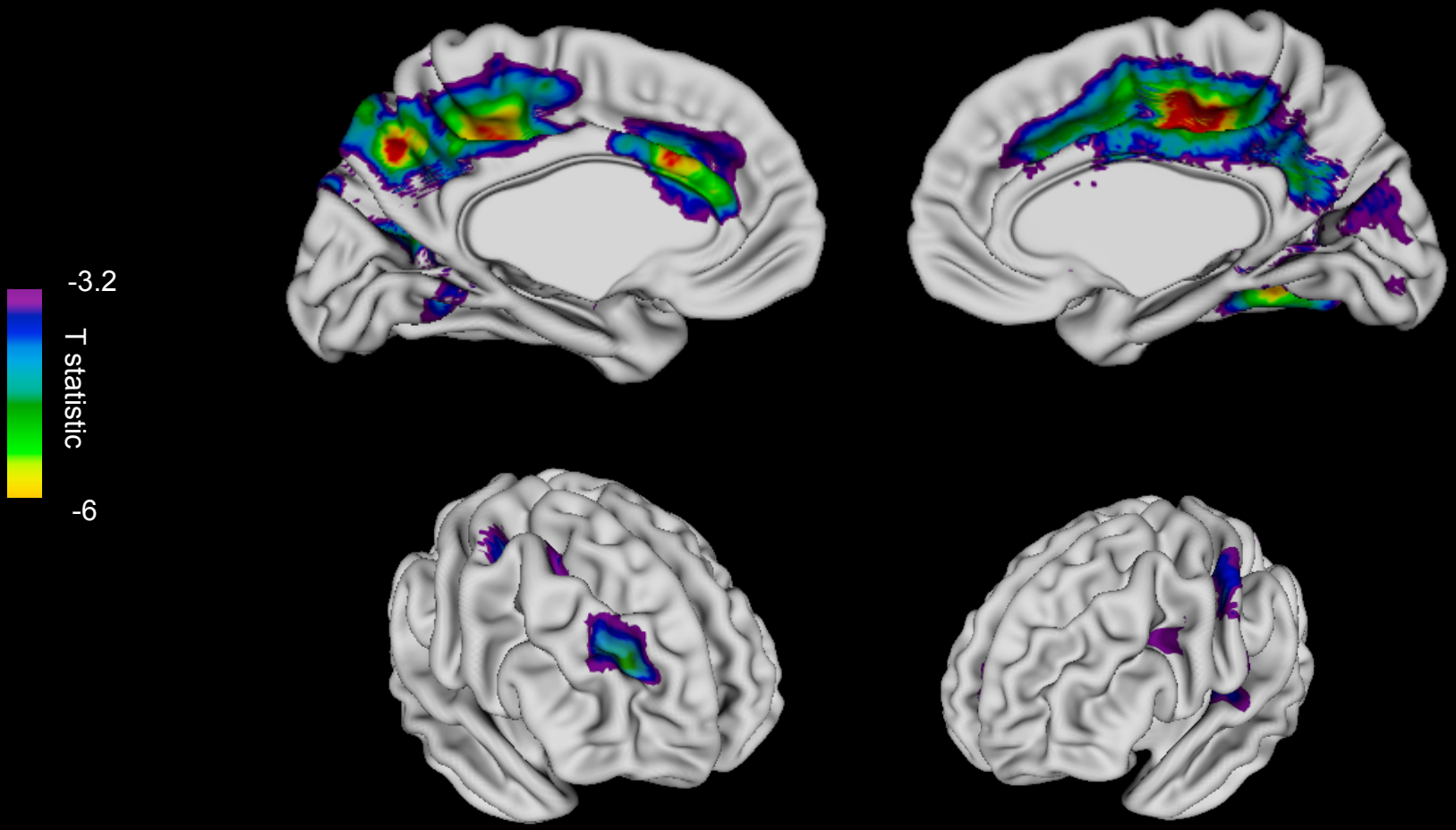
Persistence → divergence

Measure: thickness of the cortical cortex

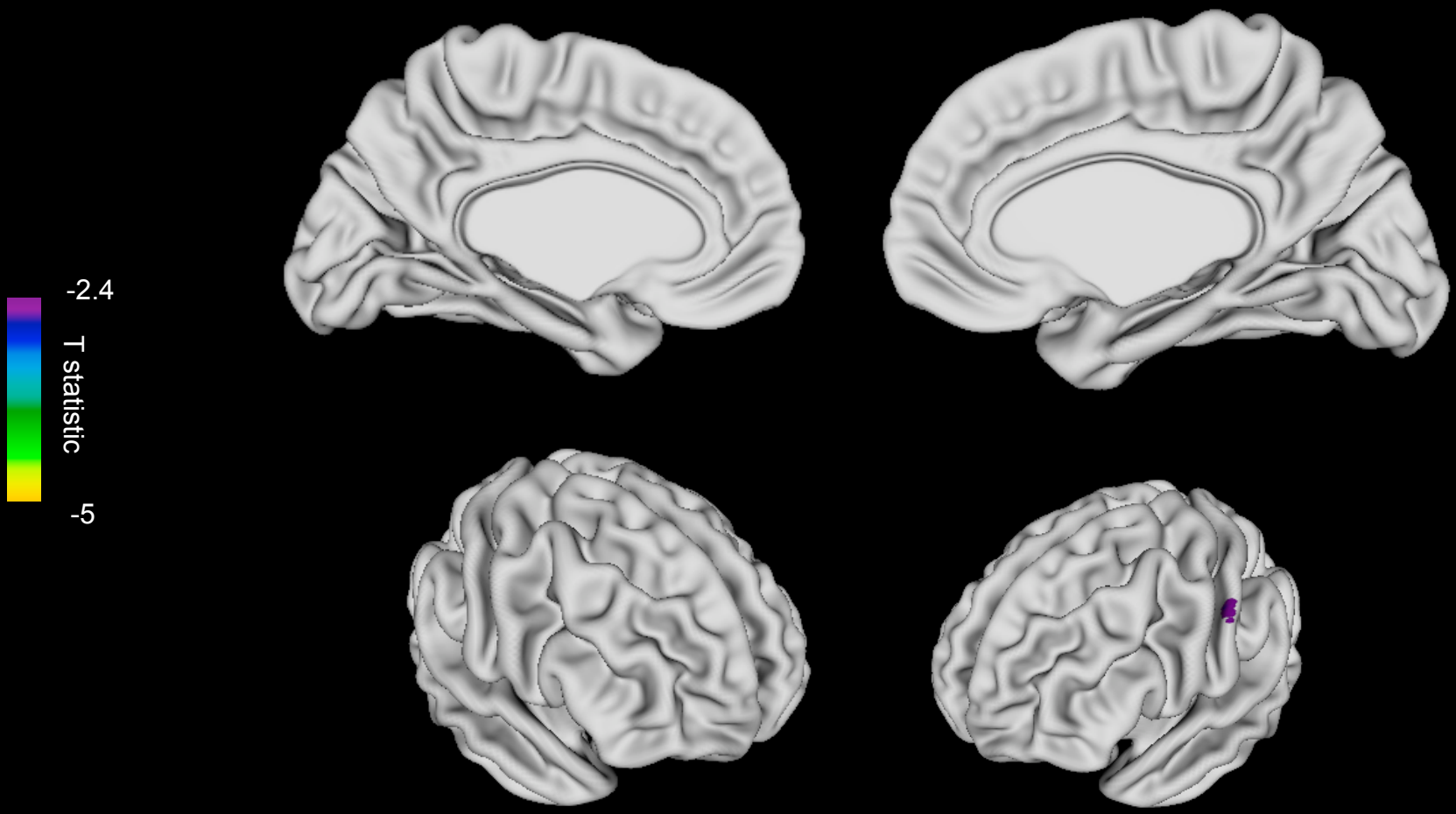
Shaw et al, 2013, Biol Psychiatry

Inattentive symptoms and cortical slopes

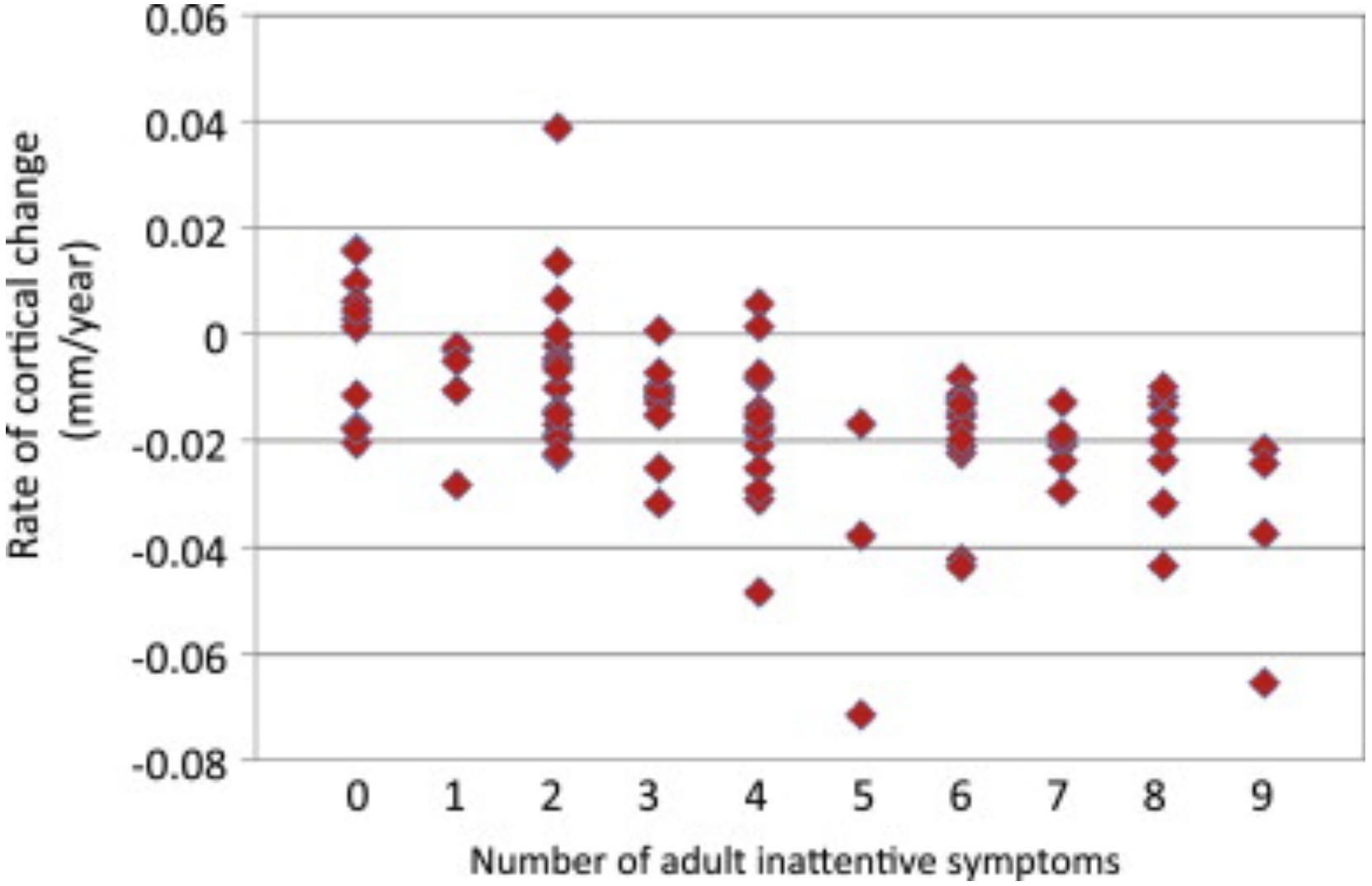
For each increase of one symptom of adult inattention, rate of adolescent cortical thinning increases by 0.0018mm/year (SE 0.0004); ~5% change over mean rate of thinning for entire group



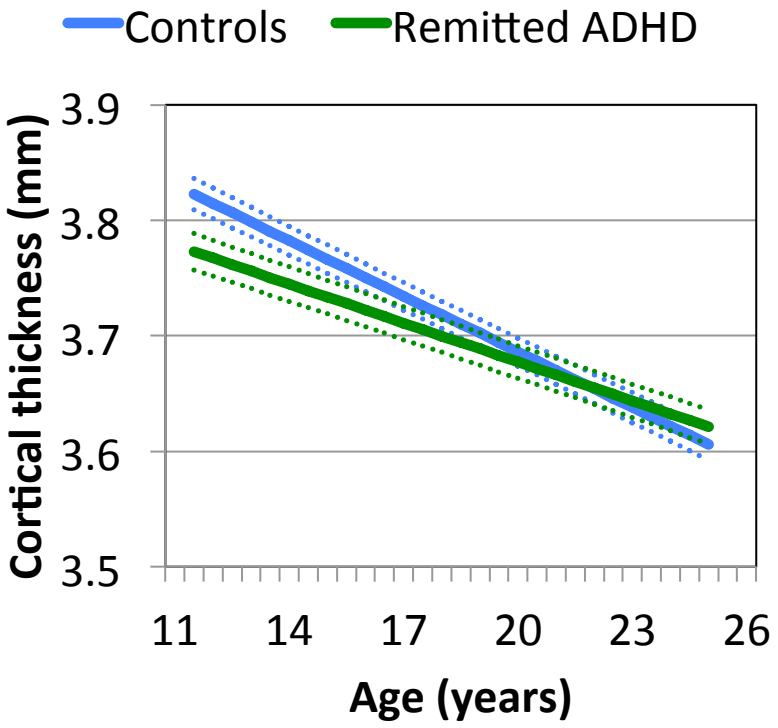
No links with hyperactive-impulsive symptoms



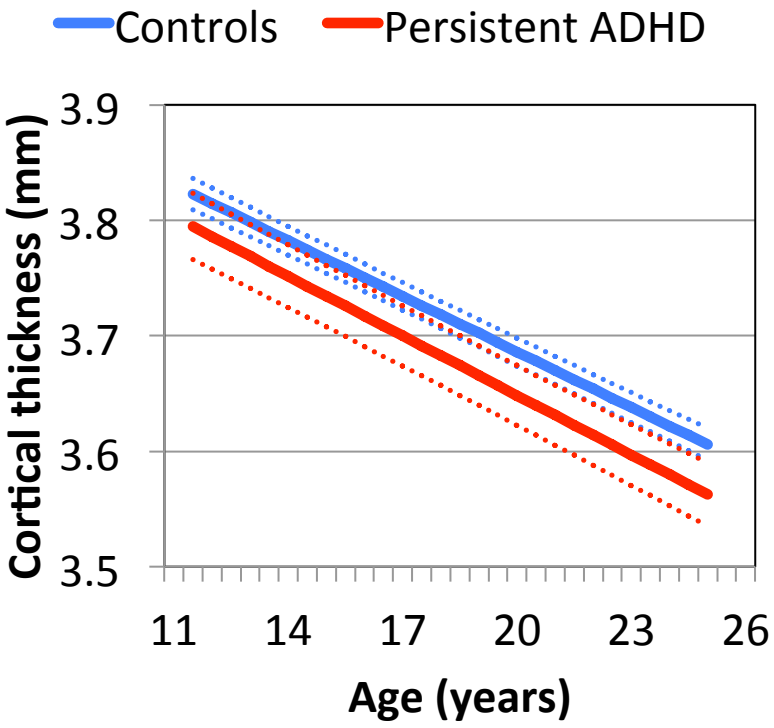
Rates of medial PFC change and adult inattention



Adolescent trajectories and adult outcome



Slope difference, p<0.002



Slope difference, p=0.11

Study 2. Conclusions

- Trajectories linked with inattention localize to cortical regions which are key hubs in networks supporting:-
  - Dorsal attention (Intraparietal sulcus/FEF)
  - Working memory (fronto-parietal)
  - Motor planning and execution (SMA/sensorimotor cortex)
  - Default mode network (posterior cingulate/precuneus)

- Developmental links between the cerebral cortex and deeper structures
  - Patterns of coordinated, correlated change in thalamus and cortex differentiates between outcome groups in ADHD (Sudre et al, In prep).

Summary: developmental trajectories

- Childhood ADHD
  - ADHD is characterized by differing forms of atypical development of the prefrontal cortex and striatum

- Adult ADHD
  - Cortical 'hubs' of key brain networks
    - remission = normalization of 'attention' network
    - persistence = fixed anomalies (hint of divergence)
  - Atypical structural connectivity within the networks

Translating the findings- predicting outcome?

- Hypothesis: Normalizing trajectories of the 'attention-network' predict clinical improvement.
- Study: do trajectories on 260 children defined from 3 MRI scans predict later outcome?
- Including white matter tracts linking the network, and measures of brain activation during attention-demanding tasks (fMRI/MEG)
- Moderation by genotype?
- Collaborative effort: two centers planning to collect similar data (available end 2018).

Thank you

- NHGRI
  - Eszter Szekely
  - Gustavo Sudre
  - Amy Wharton
  - Bethany Watson
  - Saadia Choudhury
  - Cristina Justice, Alec Wilson
- NIMH
  - Wendy Sharp
  - Judy Rapoport
- Toronto
  - Mallar Chakravarty
  - Jason Lerch
- UMC Utrecht
  - Sarah Durston
- Erasmus MC, Rotterdam
  - Henning Tiemeier